Statistical Segmentation of Biological Sequences

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The Biological Sequence Segmentation Problem

- Two motivating problems:
  - **HT segments** (genomic islands) and **lineage-specific segments** (backbone) in bacterial DNA.
    * HT segments have different statistics from backbone.
    * Pathogenic genes frequently found near HT segment boundaries.
    * Gene-finding algorithms do not perform well in regions where statistics differ significantly from backbone.
    * Scoring problem even more severe for computational search of short regulatory elements.
  - **Mesoscopic description of genome**: ‘Local’ statistics vary along DNA sequence. Break long sequence into intermediate length segments, based on ‘discernible’ changes in statistics. Coarse-grained description.

- DNA polymerization along $5' \rightarrow 3'$ direction builds directionality into sequence. Biases in dinucleotide and codon frequencies. Model as **Markov chains** rather than Bernoulli chains with extended alphabets.
Markov chains

- State $x_i$ of Markov chain at sequence position $i$ can take on values in alphabet $S$ of size $S$. **Example.** For DNA sequences, $S = \{A, T, C, G\}$, and $S = 4$.

- Markov chains generated probabilistically. Existing subsequence extended by attaching $x_0$ to end of subsequence with transition probability

  $$p(x_0|x_{-1}x_{-2}\cdots x_{-K}).$$

- Markov chain of order $K$ if $p(x_0|x_{-1}x_{-2}\cdots x_{-K'}) = p(x_0|x_{-1}x_{-2}\cdots x_{-K})$ for all $K' \geq K$.

- Transition probabilities can be organized into transition matrix

  $$\mathbb{P} = [p_{ts}], \quad s = 1, \ldots, S, \quad t = t_1\cdots t_K \in S^K.$$

- Equilibrium distribution $\pi = (P_1, \ldots, P_k, \ldots, P_{sk})$ such that $\pi\mathbb{P} = \pi$, $P_k =$ probability of finding $k$th $K$-mer in stationary Markov chain.
Classification of Segmentation Schemes

- Matrix of segmentation schemes in literature:

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<thead>
<tr>
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<th>single-pass</th>
<th>recursive</th>
<th>local</th>
<th>global</th>
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<tbody>
<tr>
<td>sliding window average</td>
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<td>DNA walk</td>
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<td>dynamic programming</td>
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<td>hidden Markov model</td>
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- All schemes rely on entropic measure of statistical dissimilarity, whether:
  - computed directly; or
  - in the form of inner product between quantized vectors of probabilities.
The Jensen-Shannon Divergence

- Given length-$N$ sequence $x = x_1x_2\cdots x_N$, $x_i = A, C, G, T$, assume composed of $M \geq 1$ Markov chains with boundaries at $i_1, \ldots, i_{M-1}$. $M$-segment sequence likelihood given by

$$P_M(x; i_1, \ldots, i_{M-1}; \hat{p}_1, \ldots, \hat{p}_M) = \prod_{m=1}^{M} \prod_{t \in S^K} \prod_{s=1}^{S} (\hat{p}_t^m)^{f_{ts}^m} ; \quad \hat{p}_t^m = \frac{f_{ts}^m}{\sum_{s'} f_{ts'}^m}.$$  

- Jensen-Shannon divergence

$$\Delta_M = \log \frac{P_M}{P_1} = - \sum_{t \in S^K} \sum_{s=1}^{S} f_{ts} \log \hat{p}_t + \sum_{m=1}^{M} \sum_{t \in S^K} \sum_{s=1}^{S} f_{ts}^m \log \hat{p}_t^m;$$

$$f_{ts} = \sum_{m=1}^{M} f_{ts}^m, \quad \hat{p}_t = \frac{f_{ts}}{\sum_{s'=1}^{S} f_{ts'}}$$

is symmetric relative entropy providing quantitative measure of ‘goodness-of-fit’ of $M$-segment model over 1-segment model.
Segmentation with a Pair of Sliding Windows

- For a single sliding window of length $n$, spatial resolution decreases with $n$ while statistical significance increases with $n$.

- Solution: To not compromise spatial resolution, use an adjoining pair of sliding windows, each of length $n$.

- Compute $\Delta_2(i)$ using $\hat{P}_L$ in left window and $\hat{P}_L$ in right window as function of sequence position $i$ of centre of pair of windows.

- Segment boundaries appear as peaks in $\Delta_2(i)$. Strength of peak measure of statistical difference between the segments it separates.
The interval $(0, 40000)$ in the *E. coli* K-12 MG1655 genome ($N = 4639675$), showing the $K = 0$ Jensen-Shannon divergence spectrum for $n = 1000$. Annotated genes on the positive (red) and negative (green) strands are shown below the graph.
Recursive Jensen-Shannon Segmentation

- **STEP 1 (Segmentation):**
  - Given sequence \( x = x_1x_2 \cdots x_N \), compute 2-segment Jensen-Shannon divergence \( \Delta_2(i) \) as function of cursor position \( i \).
  - Find \( i^* \) such that \( \Delta_2(i^*) = \max_i \Delta_2(i) \). The best 2-segment model for \( x \) is \( x = x_Lx_R \), where \( x_L = x_1 \cdots x_{i^*} \) and \( x_R = x_{i^*+1} \cdots x_N \).

- **STEP 2 (Recursion):** Repeat **STEP 1** for \( x_L \) and \( x_R \).

- **STEP 3 (Termination):** 1-segment model selected over 2-segment model if:
  - **Hypothesis Testing:** probability of obtaining divergence beyond observed \( \Delta_2 \) greater than prescribed tolerance \( \epsilon \); or
  - **Model Selection:** information criterion (e.g. AIC, BIC) for 2-segment model greater than that for 1-segment model.
Jensen-Shannon divergence spectrum of order $K = 3$ over the entire genome of \textit{E. coli} K-12 MG1655 ($N = 4639675$ bp). The first segment boundary to be obtained in this first stage of recursive segmentation is shown by the red arrow.
Segmentation Optimization

- Two procedures to optimize segment boundary $i_m$ if we are allowed to move only one segment boundary at a time:

- First-order update: Compute $\Delta_2^m(i)$ for supersegment $(i_{m-1}, i, i_{m+1})$, and choose $i_m = i^*$, such that $\Delta_2(i^*) = \max_{i_{m-1} < i < i_{m+1}} \Delta_2(i)$, to be new position of segment boundary.

- Second-order update: Compute $\Delta_2^{m-1}(i)$ for supersegment $(i_{m-2}, i_{m-1}, i)$ and $\Delta_2^{m+1}(i)$ for supersegment $(i, i_{m+1}, i_{m+2})$, and choose $i_m = i^*$, such that

$$\Delta_2^{m-1}(i^*) + \Delta_2^{m+1}(i^*) = \max_{i_{m-1} < i < i_{m+1}} \left[ \Delta_2^{m-1}(i) + \Delta_2^{m+1}(i) \right],$$

to be new position of segment boundary.

- Segment boundaries $\{i_m\}_{m=1}^M$ updated serially, or in parallel.

- Optimized recursive segmentation: Right after STEP 1 (Segmentation), optimize segmentation using first- or second-order update algorithm.
Conclusions & Further Works

• In conclusion, we have:
  – Developed segmentation scheme using a pair of sliding windows;
  – Developed optimization algorithms for recursive Jensen-Shannon segmentation scheme; and

• Further works:
  – Mean-field analysis of sliding window segmentation scheme: mean-field line-shape and match filtering;
  – Mean-field analysis of recursive segmentation scheme: identified problem of context sensitivity;
  – Developed new termination criterion based on intrinsic statistical fluctuations.
  – Incomplete segmentation misleading, cluster terminal segments instead to obtain coarser scale description of genome. E.g. to distinguish lineage-specific regions arising from HGT and the genetic backbone.
  – Multiple sequence clustering for comparative, phylogenetic studies.